

**REMARKS**

The foregoing amendment amend claims 16, 19, 20, 22, 27, 30, 33 and 36, cancels claims 26, 29 and 32 and adds claims 38-42. Pending in the application are claims 16-22 and 24-25, 27-28, 30-31 and 33-42, of which claims 16, 19, 20, 22, 37, 38 and 39 are independent. The following comments address all stated grounds for rejection and place the presently pending claims, as identified above, in condition for allowance.

Independent claims 16, 19, 20 and 22 are amended to specify that the step of isolating cells comprises conveying a mixture including cells having the desired phenotype and cells that do not have the desired phenotype through a sorting channel of the microfluidic cell sorting device and applying a pressure pulse to a cell having the desired phenotype to deflect the cell having the desired phenotype into a first outlet of the sorting channel while cells not having the desired phenotype flow into a second outlet of the sorting channel, as set forth in cancelled claims 26, 29, 32 and 35.

New independent claim 38 is directed to a method of isolating a subpopulation of cells that recites the subject matter of previously presented claim 16 and further recites a step of measuring a velocity of a cell having the desired phenotype before isolating the cell. Support for the new claim can be found throughout the application as originally filed, at least, for example on page 17, lines 7-15.

New independent claim 39 is similar to claim 16 and further specifies that the step of applying a pressure pulse comprises deflecting a meniscus formed by fluid at an intersection between a side channel in communication with the sorting channel and a sealed chamber positioned adjacent to the side channel. Claims 40-42 depend from claim 39 and recite additional patentable subject matter supported throughout the original application. *No new matter is added.*

Amendment and/or cancellation of the claims is not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicant reserves the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

Claim Rejections Under 35 USC § 103

In the Office Action, the Examiner rejects claims 16-22 under 35 U.S.C. §103(a) as being unpatentable over Diessel et al. (U.S. Patent Number 5,837,200) in view of Furlong (6,482,652). The Examiner considers that it would be obvious to modify Diessel to sort according to phenotype in view of the Furlong reference, which discloses sorting embryos or other large biological particles according to phenotype. Applicants respectfully traverse the rejection and submit that the pending claims distinguish patentably over the cited references.

The Diessel reference discloses a sorting device that sorts particles based on magnetic marking, but, as recognized by the Examiner, also fails to disclose sorting of particles based on phenotype or a cell cycle stage specific marker. The Diessel reference also fails to disclose applying a pressure pulse to a selected cell to perform a sorting process, as now set forth in claims 16-22, 24-25, 27-28, 30-31 and 33-37.

According to the Examiner, because the Furlong reference discloses sorting embryos according to phenotype, the claims are obvious. However, the Furlong reference is not readily combinable with the Diessel reference, because the Furlong reference is directed to large particles that could not be sorted using a *microfluidic* cell sorting device. As set forth on the first paragraph on page 8 of the application, a channel in a microfluidic system has cross-sectional dimensions in the range between about 1.0  $\mu\text{m}$  and about 500  $\mu\text{m}$ , preferably between about 25  $\mu\text{m}$  and about 250  $\mu\text{m}$  and most preferably between about 50  $\mu\text{m}$  and about 150  $\mu\text{m}$ .

In contrast, the Furlong reference is concerned with “the sorting of biological particles that are too large to be sorted by conventional flow cytometry” as set forth on column 2, line 65-67. The particles sorted by Furlong comprise “at least about 10 cells” and may have a size that would not fit within a microchannel of a microfluidic sorting device. See column 2, line 65 through column 3, line 6.

In addition, the cited references do not disclose sorting a particle by applying a pressure pulse to a selected cell. In fact, the Furlong reference teaches away from the subject matter of claim 1, by “eliminating the need for deflection” when sorting particles (column 1, lines 39-41). Furlong relies on a switching mechanism 40 that controls the position of a collection conduit 46

between two set points in order to separate particles, but does not employ a pressure pulse. As described above, the Diessel reference relies on magnetic attraction to sort particles, rather than a pressure pulse.

According to the Examiner, the Zold reference discloses sorting by pressure pulse via a meniscus interface and is therefore combinable with the Diessel reference and the Furlong reference to render the subject matter of claim 15-22, 26, 27, 29, 30, 32, 33 and 35-37 obvious. However, the Zold reference does not rely on a pressure *pulse*, i.e., a momentary flow disturbance, to sort particles. Rather, the Zold reference paralyzes flow through an outlet channel 16 or 17 to displace an entire flow stream, rather than a single, selected particle. In Zold, a gas bubble generated between electrode pairs *blocks* flow through a selected outlet channel to change the *overall* flow of particles, without applying a pressure pulse to a single particle at a time. The gas bubble created in Zold does not deflect a particle from a stream. In Zold, the device returns to steady-state only when the outlet channel becomes unblocked. In contrast, the present invention *automatically* returns to steady state after application of the momentary deflecting impulse. See column 17, lines 2-40, column 18, lines 47-54 and, column 19, lines 12-60 of Zold. Therefore, the claimed subject matter is different from the subject matter described in the Zold reference.

The cited references, alone or in combination, do not teach or suggest the claimed method of sorting, set forth in claims 16-22, 24-25, 27-28, 30-31 and 33-37. Moreover, the Examiner has failed to establish a *prima facie* case of obviousness, because he has not pointed to any motivation to combine and/or modify the teachings of the cited references to render the conclusion that the claims are obvious, as required under 35 U.S.C. §103. Therefore, the rejection based on 35 U.S.C. §103 is improper and should be withdrawn.

Applicants respectfully submit that motivation to modify the teachings of the cited references is lacking. Under U.S. law, even if a combination of the references teaches every element of the claimed invention, without a motivation to combine, a rejection based on a *prima facie* case of obvious is improper.

In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to

suggest making the claimed substitution or other modification. The prior art must provide the motivation to make a change to its own teachings to arrive at the invention under rejection. That is, it is not sufficient that the prior *could be* so modified; instead the prior art must teach or suggest that the prior art *should be* so modified.

It is well-established law that the motivation to modify the teachings of a reference or to combine references must come from the references themselves, and cannot be derived from the teachings of the application under examination. However, none of the cited references, alone or in combination, teaches or suggests the claimed invention, or provide any motivation for modification or combination of their teachings. Therefore, the claims are patentable over the cited references and in immediate condition for allowance.

Moreover, the cited references do not disclose a method that includes sorting and screening and/or modification of sorted cells on the same microfluidic device, as set forth in claims 24-25, 31 and 34.

The cited references also fail to disclose removing isolated cells from a microfluidic cell sorting device and transplanting the isolated cells, as set forth in claim 28.

#### New claims

New independent claim 38 is directed to a method of isolating a subpopulation of cells that includes a step of measuring a velocity of a cell to be sorted, a feature lacking in the prior art.

New independent claim 39 recites a method of isolating a subpopulation of cells by deflecting a meniscus formed by fluid at an intersection between a side channel in communication with the sorting channel and a sealed chamber positioned adjacent to the side channel. The deflection of the meniscus applies a pressure pulse to a cell having the desired phenotype to deflect the cell having the desired phenotype into a first outlet of the sorting channel while cells not having the desired phenotype flow into a second outlet of the sorting channel. As described above, the cited references, in particular the Zold reference, lack a teaching or suggestion of using a pressure

pulse to deflect a cell from a stream of cells. In addition, the Zold reference does not create a meniscus between a fluid and a sealed chamber, because the buffer cavities 20 and 21 are not sealed and are simply “large holes...drilled into the body 1 of the device quasi perpendicularly into its top surface 4”, as set forth in column 20, lines 41-44 and shown in Figures 1 and 2. No meniscus is employed or present in the device of Zold to deflect a particle. Therefore, claims 39-42 are patentable over the prior art.

Dependent claim 42 recites additional patentable subject matter, by reciting the step of measuring a velocity of a cell, which, as described above, is patentable over the prior art.

For at least these reasons, pending claims 16-22 and 24-25, 27-28, 30-31 and 33-42, distinguish patentably over the cited references. As such, Applicants request reconsideration and withdrawal of the instant rejections.

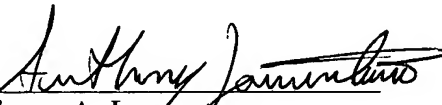
**CONCLUSION**

In view of the above amendment, applicant believes the pending application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. If, however, the Examiner considers that obstacles to allowance of these claims persist, we invite a telephone call to Applicant's representative.

Applicants believe no fee is due with this Amendment. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. TGZ-021CP2 from which the undersigned is authorized to draw.

Dated: October 12, 2005

Respectfully submitted,

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